PROPHYLACTIC INOCULATION AGAINST TYPHOID FEVER IN THE FOURTH MILITIA DIVISIONAL AREA OF CANADA*

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THE efficiency of an army in the field to-day depends largely upon the factors that have made armies efficient in the past,—training, generalship, equipment, and the physical condition of the troops. The constant developments that have taken place along each of these lines have in most instances been gradual, though at times they have been almost miraculously sudden. This is especially true of certain aspects of the medical sciences. These developments have come with specialization in the arts and sciences of war; a specialization in those scientifically proven measures which adapt themselves to the peculiar demands of a force that must at all times be mobile.

In this specialization medicine, in the broad sense of the word, has received most careful consideration. The medical interest in the fighting man has gradually broadened from that of the earlier days, when only those wounded or ill in camps were cared for, to an interest which in its scope deals with the recruit from the time of his enlistment and even with his family before him, all through his military career, and with his remains when he has paid the toll of war. This interest can in no sense be looked upon as a narrow interest. It is an interest as broad as medicine itself, and commands the best thought and the best energy of the best men in all of its branches.

Military authorities early realized the practical benefits to be derived from the application of the truths learned by the study of hygiene and preventive medicine, and have in general, so far as is

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possible and practicable, adapted these measures to their fighting forces. The practical application of this comparatively recently developed science has added most substantially to the efficiency of armies and has developed a feeling of security among officers and men that counts for increased efficiency. The successful operation of those preventive measures that are applied to armies in the field to-day may play an important part in the final outcome of the present war. They might even determine it. Uncontrolled epidemics of certain diseases might take a heavier toll than shrapnel and rifle bullets. For this reason the preventive measures that to-day are so scrupulously enforced by the military authorities mean, when analyzed, a practical demonstration on a large scale of the chief principles of preventive medicine and hygiene. To a particular phase of one branch of preventive medicine—prophylactic inoculation against typhoid fever—we wish to refer in some detail.

It is not necessary that we review the convincing statistics that have been published by army officers of Great Britain and the United States, nor is it necessary to go into the history of antityphoid inoculation. It is well known to all. But it has had its difficulties. These difficulties have gradually been surmounted until to-day an army unprotected against typhoid fever is an army whose efficiency, however great to-day, may be materially diminished to-morrow. The Militia Department of Canada early realized this and antityphoid inoculation in the Canadian Expeditionary Force has kept pace with recruiting.

In one militia divisional area we have had some part in this fight against typhoid fever, and wish here to record some of the data in regard to it.

One of us, anticipating its possible need in the present great war, obtained last summer a culture of *B. typhosus* from Sir William Leishman's laboratory in London. This was a transplant from the same culture used by him in the preparation of anti-typhoid vaccine for the British Army and by the United States Army in the preparation of the vaccine used by them—a culture selected chiefly for the reason that its efficiency in terms of protective reaction on the part of the body is high, and the symptoms following its inoculation are slight.

In the preparation of the vaccine made by us we have grown the organisms in bulk, on plain agar corrected to 1·5 per cent. acid to phenolphthalein. The agar is made stiff, 2·4 per cent., put into Blake bottles, slanted, and allowed to cool. By using an agar of this percentage the organisms may be easily removed from the medium without tearing pieces of the medium off. The use of agar slants as

made above has the advantage that accidental contaminations are more easily recognized than when the organisms are grown in some fluid medium, and the possible objection to injecting peptone-containing fluid avoided. After the Blake bottles have been inoculated and allowed to remain in the incubator at 37° C. for eighteen hours, they are removed and there is added to each of them 5 c.c. of sterile normal salt solution. By means of a properly bent platinum needle the surface growth is easily scraped off and mixed in the salt solution at the bottom of the bottle. The mixture is then transferred by means of a sterile pipette to a sterile culture tube which has been drawn out in its upper third. This tube is now sealed in the flame and placed in a vaccine shaker for fifteen minutes, when the colonies and clumps of organisms are thoroughly broken up. All except 2 c.c. of this mixture, which is kept for bacteriological examination, is added to a flask containing a known quantity of sterile normal salt solution, and thoroughly mixed. The amount of sterile normal salt solution used is optional. We have used a known quantity in order that we might calculate the number of cubic centimetres of finished product that it was necessary to be prepared for. As the amount of vaccine made at one time has, as a rule, been five litres, the amount of sterile salt solution to which the mixture of organisms is added, has been 500 c.c. We have used 500 c.c. as this amount is easy to handle.

In order that the bacterial count of this mixture may be exact, before the original bacterial mixture is added to the sterile salt solution, there is removed from it as many cubic centimetres as there are cubic centimetres of bacterial mixture. This mixture contains far too many organisms to be used as it is, but it is easy to apply heat to this amount, and from it the final dilutions are readily made.

The number of organisms per cubic centimetre of this mixture is now determined. We have done this by means of a specially made counting chamber, as in our hands this method is more accurate than the others we have tried.

The two cubic centimetres left in the culture tube containing the original bacterial mixture is taken for bacteriological examination in order that one may be sure that the culture used is a pure culture.

The method we have employed for killing organisms is as follows. The flask containing the bacterial mixture is placed in a water bath with heat regulated so that the temperature of the mixture within the flask is kept at 54° C. This is made easy and accurate by putting into a second flask, of the same size and shape as the one containing the bacterial mixture, as many cubic centimetres of normal salt solution as there are cubic centimetres of fluid within the

flask containing the bacteria. A thermometer is passed through the cork in the flask containing the normal salt solution and extended down into the central portion of its contents. This control flask and the one containing the bacterial mixture are fastened side by side in a wire basket which is lowered into the water bath so that the water in the bath comes well above the fluid in the flasks. If the flasks are gently shaken while in the bath, the heat from the water in which they are placed is more uniformly transmitted to the fluids within them. The fluids in the flasks are kept at 54° C. for 45 minutes, when the flasks are removed and allowed to cool. Previous to heating the bacterial mixture, 500 c.c. of normal sodium chloride is placed in each of a number of flasks. These are sterilized in the autoclave and to each of them 0·25 per cent. of carbolic acid is added. The flasks are thoroughly shaken in order that the carbolic acid may be uniformly distributed. As the number of organisms per cubic centimetre in the flask which has been heated is known, it is easy to estimate the number of cubic centimetres of the heated bacterial mixture that it is necessary to add to each flask containing the carbolized normal salt solution in order to bring its bacterial content up to 1,000 million organisms per cubic centimetre. Before the correct number of cubic centimetres of the bacillary emulsion is added, an equal amount of fluid is removed from each flask. A few cubic centimetres of the fluid containing the organisms, to which heat has been applied, is again tested bacteriologically. Both ærobic and anærobic cultures are made.

The completed vaccine may be put into containers at once or stored in the flasks in bulk. Whether it is to be bottled or kept in bulk to be bottled later, a final bacteriological examination is made after it has been in its final containers for three days. Besides making ærobic and anærobic cultures we have examined for *Bacillus tetanus*. We have never found contaminating organisms but once, when *B. subtilis* developed on one of the agar slants. It was readily recognized and the Blake flask in which it grew was discarded. We feel that repeated bacteriological examinations should always be made in order that every possible precaution may be taken to ensure the sterility of the finished product. It has been our rule that none of the vaccine is to be used before three weeks, or after four months, from the date of its preparation. An antityphoid vaccine at or beyond three weeks after its preparation seems to be more efficient than a freshly prepared one.

Antityphoid inoculation is not absolutely compulsory in the Canadian Expeditionary Force; the men are told of its advantages and are strongly advised to avail themselves of the protection it

offers. Insofar as we are able to learn, not a single individual of the Fourth Militia Divisional Area under the direct control of the A.A.D.M.S. has persistently refused to receive his inoculation.

The method of handling troops and the technique used in giving the inoculation, as practised by Major Muckleston and Captain McKim, have been as follows: when a body of troops is brought up for inoculation, they are carefully and plainly told of its advantages and are also as carefully told of the symptoms which are to be anticipated. No one is inoculated who is in any sense ill; acute rhinitis and the recent extraction of teeth have in a number of instances postponed the administration of the vaccine. The officer in command of the men inoculated is instructed to relieve them from duty for forty-eight hours and the inoculated men are given careful instructions in regard to their duty to themselves. They are to go to their homes or barracks at once, abstain absolutely from alcoholic drinks, take no violent exercise, and go early to bed.

The method of handling troops in large numbers is important. Where large bodies of men are to be handled, time must be considered but not at the expense of safety and accuracy. Discomfort to the individual, however slight, must be carefully considered.

The men are lined up in single file with arms bared to the shoulder. An area on the arm 10 cm. in diameter is painted with iodine, and precautions are taken to prevent touching this spot. 5 c.c. Record syringes with a number of needles are sterilized by boiling. Where bottles are used as containers for the vaccine, their caps are sterilized with alcohol or carbolic, and absorbent cotton soaked in the solution used is kept over them. The hypodermic needle attached to the syringe is plunged through the cap and the syringe filled. By using a 5 c.c. syringe time is saved, as ten first inoculations or five second inoculations can be made from one syringe full. After each inoculation the needle is removed and another sterilized needle is attached by means of sterile forceps.

The site of inoculation has in all cases been the arm, about 10 cm. directly above the external condyle of the humerus. In right-handed men the left arm is used; in left-handed men the right. This point is selected for the reason that it is not too close to the large nerve trunks and large blood vessels. The injection is made subcutaneously; never into the muscle, as muscular injections are more painful than subcutaneous ones and for this reason interfere too much with the movements of the arm.

In most instances two inoculations, ten days apart, have been given. At the first, one-half c.c or 500 million dead organisms are

injected; at the second, one cc. or 1,000 million organisms. In a few instances the more ideal procedure of three inoculations has been employed. This has applied to certain individuals and to two units, those commanded by Col. H. S. Birkett and Lieut-Col. R. P. Campbell.

The reaction following the inoculation has been carefully watched by Major Muckleston, A.M.C., and Captain McKim, A.M.C., whom we thank for the data collected by them. The reactions have varied greatly. They may be divided into two groups, local and general. Both of these have varied within comparatively wide limits.

The milder local reactions consist of slight swelling and redness with slight tenderness about the point of inoculation. The more severe local reactions are characterized by swelling and redness of greater extent. In a few instances these have extended throughout the greater extent of the surface of the arm into which the injection was made. The pain likewise varied but in no instance has it been severe.

A most careful watch has been kept for infection at the site of inoculation. In no case has there been the slightest evidence of it.

The constitutional symptoms have likewise varied within wide limits. In most cases there is a feeling of depression within the first five hours after inoculation. Frequently this has been accompanied by headache, general malaise and pains in the joints. Several individuals who had had typhoid fever a number of years previous to their inoculation had pain in the joints, which they insisted was of the same character as that experienced during the early period of their typhoid fever. In a very small percentage of cases the general malaise with headache has caused sufficient inconvenience to keep the case in bed the following day. A certain percentage of cases have had a rise in temperature. In most instances this has been slight, though in one case it reached 103° F. A few individuals have complained of itching of the skin. It has been noted in this series as in others that the reaction is generally comparatively severe in those who have had or have chronic malaria.

A very few cases have had a slight diarrhœa following their inoculation.

One of the arguments of that group of individuals who are opposed to prophylactic inoculation in general, is that an inoculated individual is more susceptible to acute infectious diseases than an uninoculated one. In this series of over seven thousand cases there seems to be no reason for concluding that, in this comparatively large series, there has been any relation between antityphoid inoculation and increased

susceptibility to infection. The possibility of an increased susceptibility to infection was considered, and precautions were taken to minimize it. All inoculated individuals have been relieved from their duties for forty-eight hours and certain very definite instructions given to them. In the series under consideration, the inoculated men were not more susceptible to rhinitis, pharyngitis and tonsillitis than the uninoculated. It might be further stated that there has not been a case of typhoid fever develop in the troops since inoculation began, although there have been a number of cases in the cities where the men were in barracks.

In one instance it was advisable to inoculate a nurse ten days after an operation for appendicitis. There was a slight rise in temperature following the inoculation, but the wound showed no change and there was nothing in her convalescence even to suggest that her antityphoid inoculation had interfered in any way with her convalescence.

There has been considerable interest in the advisability of inoculating individuals who have had tuberculosis. We have had three instances where inoculations were given to men who had been treated for this disease. In these men the diagnosis was without question. Each of them had received sanitarium treatment and the lesions pronounced healed or inactive. Two of them were physicians. The reactions in these three cases were not any more severe than in the other men, nor has there been any untoward result from the inoculation. We would not leave the impression that we advocate the inoculation of those who have active tuberculosis. On the other hand, we would oppose it on the principle that such cases should not be subjected to any mental or physical conditions that might lower their resistance, if such could possibly be avoided. When one considers the high percentage of cases that have died of some other disease and yet show at post mortem evidence of tuberculosis—active, inactive, or healed,—it seems fair to assume that a considerable number of soldiers would show the same. The physical examination of troops to-day is done with such care that tubercular lesions, save the smallest inactive or healed ones, rarely pass undetected. Should a man with an inactive or an active lesion be taken into the army, and these lesions later extend locally, or from them a miliary tuberculosis result, antityphoid inoculation cannot be held wholly responsible for them. Infantry drill, rifle drill, and route marches test the endurance of the best of men, and surely nothing could favour more the development of activity in inactive lesions or increase the activity of active ones.

Circumstances have been such that all our vaccine has been put

in bottles closed with rubber caps. The emergencies of the present war have been such that regular vaccine rubber caps could not be secured. As a substitute we have used very heavy finger cots, and have found them perfectly satisfactory. In fact we know of no better rubber cap if it is properly prepared. We have prepared them as follows: the powder which adheres to them is removed. They are then soaked in weak carbolic acid for four hours, after which they are thoroughly washed in several changes of distilled water and rolled as follows. The cot is placed over the index finger, closely rolled upon itself completely up to the tip, when the tip is inverted. This gives a thick collar of rubber with a single thickness of rubber to close the mouth of the bottle. The rolled finger cots are now thoroughly sterilized by boiling, when they are ready to apply to the bottles. The sterile caps are removed from the water in which they were sterilized by sterile forceps, and forced over the necks of the bottles. The collar which results from rolling the cot upon itself fits tightly about the neck of the bottle. The comparatively thick rubber cap is easily punctured, and the punctured holes scarcely ever leak, even before the caps are paraffined. After the caps have thoroughly dried, they are dipped into hot paraffin.

We have supplied vaccine made as above for the inoculation of over seven thousand troops, and in no instance has there been an infected arm, nor have the local or constitutional reactions been in the least alarming. Neither is there any evidence obtainable that those inoculated were any more susceptible to acute infections than the uninoculated in the same barracks.

Permission for the publication of this article has been obtained from Col. E. W. Wilson, O. C. Fourth Divisional Area, Militia Headquarters, Montreal.

A THREE months' course for war probationers has been arranged at St. Bartholomew's Hospital, London. Courses of three and six months' duration have also been arranged at University College for the same purpose. The probationers will serve in military hospitals under fully qualified nurses. Four hundred applications have been received at St. Bartholomew's Hospital although not more than forty can be accommodated.